An Open-label, Single Arm, Multicenter Study to Broaden Access to Emapalumab, an Anti-Interferon Gamma (Anti-IFNγ) Monoclonal Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life, and Long-term Outcome in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis

Protocol amendments

The following changes to the global protocol V1.0 (dated 19 September 2017) were included by amendments due to requests from the authorities:

The Protocol V1.1 for the EU (dated 12 December 2017) introduced the following changes:

- Inconsistencies between the body of the protocol, synopsis, and schedule of assessments were harmonized to ensure an optimal study conduct.
- The timing of chest X-ray assessment was moved to the Pre-conditioning visit to better reflect standard clinical practice.
- References to the new IB and updated information on ADA were added.

The protocol V2.0 for Germany (dated 24 May 2018) introduced the following changes:

- The study contact list was updated.
- It was added that the primary objective is to gather additional efficacy data on emapalumab in pHLH patients, and efficacy was removed from the first the secondary objective.
- The timeframe for the medical supervision of the infusions was extended from 1 hour to 2 hours, and it was added that active infections, as per patient's clinical presentation, have to be carefully followed over time.
- Viral load positivity, in particular for EBV, CMV and adenovirus, and evolution, was removed from the exceptions for AE recording requirements. Quantitative monitoring (e.g., viral loads, antigenemia, and antigenuria) as relevant according to the patient's clinical presentation, requiring EBV and CMV quantitative PCR at a minimum at screening, was added.
- It was added that any emergent safety concern will be timely assessed and appropriate measure will be taken for the patients, if relevant, by an iDMC.
- Another timepoint for vital signs measurement at 2 hours after the infusion was added.
- The estimate of the blood volume to be collected throughout the study was updated.

The Protocol V1.2 for the United Kingdom (dated 04 September 2018) introduced the following changes:

- In response to comments from the British authority, the protocol section on contraception was expanded.
- As an administrative change, contact details for 2 Sponsor team members were updated.

Protocol V2.0 for North America (dated 18 July 2018) introduced the following changes:

- The study contact list was updated.
- Vital signs assessments were made more frequently during each infusion when a dose increase was applied and during the subsequent infusions in any patient who had experienced an IRR. The duration of monitoring after infusion was extended to up to 2 hours for all patients. Clinically appropriate windows were applied to these measurements.
- The required duration of TB search testing was added as a footnote to the schedule of assessments.
- In the rationale for dosing schema, simulations were updated to present the "worst-case" scenario in the dose escalation schema, based on the updated, larger dataset accumulated in emapalumab development program that was previously submitted to FDA.
- The considerations that could prompt the Investigator to increase the emapalumab dose were further clarified. A dedicated dose notification form was implemented to capture the specificities and reasoning around the Investigator decision.
- A higher flexibility around the possibility to add other HLH treatments in the first week of treatment, i.e., the use of etoposide (or other drugs), could be considered on SD6 in a patient in whom an HLH worsening or no initial response was observed after the first emapalumab dose increase on SD3. With regard to the addition of other HLH treatments later during the study, definition of "unsatisfactory HLH control" had replaced "unsatisfactory HLH improvement", in order to better reflect the clinical conditions in which the Investigator could decide so. For completeness in the guidance to the Investigator, a reference to section on decision to discontinue treatment was added.
- A window of 1 day was introduced in the circumstances of weekly emapalumab infusions, to decrease study burden for these patients who were expected to be clinically stable and likely outpatients.
- An iDMC was appointed in place of the safety management team to regularly assess the benefit/risk profile of emapalumab treatment.
- The requirement to particularly monitor signs of fluid retention and purpura was lifted, as these pathological elements were not judged to be specifically indicative of HLH. These signs and symptoms were collected in accordance with general principles of AE recording.
- To ensure correct questionnaire completion, the patient name field was removed from the questionnaire and replaced by patient ID.

The country-specific Protocols V3.0 for the USA/Canada and Germany and Protocols V2.0 for the United Kingdom and the EU (version for Italy, Spain, and Switzerland) (all versions dated 31 October 2019) introduced the following changes:

- The Sponsor name was changed from NovImmune to Swedish Orphan Biovitrum AG.

An Administrative Letter (dated 29 January 2019) provided the following clarification for the USA sites:

Following the approval of emapalumab in the USA and its commercialization as Gamifant® for the "treatment of adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy", the enrollment in USA was limited to those patients who were naïve to conventional HLH therapy.

The global Protocol V4.0 (dated 31 March 2020) introduced the following changes:

- The study contact list was updated.
- Some clinical and laboratory parameters were defined broader in accordance with the observed median age at presentation and standard laboratory practices for routine tests.
- Suggestions from FDA for special circumstances in vital signs monitoring were implemented, blood pressure monitoring was homogenized across the countries using a conservative approach, and clinically appropriate windows were applied to the vital sign monitoring timepoints.
- Further changes were introduced to minimize the study burden on these severely ill and young patients and to simplify study conduct from logistical standpoint while still collecting sufficient data.
- Based on accumulated data, infection search was adapted to be more flexible and considerate of an individual patient while still being rigorous.
- To make the Schedule of Assessments a more complete tool for sites' convenience, a reminder about AE collection timelines was inserted, and an IRR was defined in the footnote. Definition of IRRs that required increased monitoring during subsequent infusions was expanded to include relatedness to ensure meaningful and risk-based monitoring.
- Additional measurements of height/length were introduced to accommodate calculation of creatinine clearance throughout the study duration.
- The approval of emapalumab in the USA was reflected, and updated information on other HLH treatment modalities and latest data accumulated in emapalumab development program were added.
- A provision for retreatment of patients who experience HLH reactivation in the follow-up period was made.
- The 2-year and 3-year survival data collection timepoints were removed from the body of the protocol, with the intention to collect those data in a separate study to provide a comprehensive long-term follow-up across the emapalumab development program. As per the note to file (dated 23 February 2023) to protocol version 4.0, an inconsistency within the protocol was addressed, as removal of collection of survival data at the 2-year and 3-year timepoints had been omitted in the synopsis. It was clarified that survival data collection would only be performed at 1 year after either HSCT or the last emapalumab infusion (as applicable).

- A separate section was added to list study committees to improve readability and easier search for this information.
- Clarifications on testing methods used for diagnosis of pHLH and assessment of eligibility criteria were made to reflect current global practices: NK-cell degranulation test was emerged as a more readily available alternative to NK-cell activity testing, and reference to sites' laboratories units for sCD25 was made.
- The wording on sexual abstinence was expanded based on suggestions from the British authority.
- Simulations were updated to present the "worst-case" scenario in the dose escalation schema, based on the updated, larger dataset accumulated in the emapalumab development program.
- The considerations that could prompt the Investigator to increase the emapalumab dose were further clarified. Also, additional instructions were included for lowering the dose of emapalumab to provide complete guidance to the Investigator.
- Language on the drug accountability was amended to include the reference to IRT.
- It was clarified that biologic drugs were not allowed for indications other than additional HLH treatments.
- Janus kinase inhibitors were added to the list of not allowed concomitant therapies due to their mechanism of action, possibly interfering with emapalumab efficacy and safety assessment.
- More explicit guidance was provided to the Investigator on introduction of additional HLH treatments in the beginning of the study. Also, "unsatisfactory HLH improvement" was replaced with "unsatisfactory HLH control", a definition that better reflects the clinical conditions in which the Investigator could require additional HLH treatments.
- A window of 1 day was added to allow for more flexible scheduling of emapalumab infusions in the circumstances of weekly administration.
- The screening process was further detailed in the protocol. It was clarified that standard of care procedures performed before consent were accepted for screening.
  Two documents were made available and appended to the protocol in order to facilitate expeditious assessment of the patients (eligibility review form and pre-screening checklist).
- Blood sampling assessment was expanded in accordance with a German authority request.
- It was explicitly stated that race, ethnicity, and country of origin were only to be collected if allowed per local regulations.
- The safety monitoring section language was amended for clarity and to avoid any ambiguity.
- Specific references to signs of fluid retention and purpura were removed (since these data were already collected in physical examination).

- The risks and benefits considerations were updated with the latest available information, and the current IB version was referenced. References to the development risk management plan are removed.
- A minor rewording was performed in the stopping rules section to clarify the role of Sponsor in the process.
- A maximum number of dropouts was specified considering the ongoing pandemic.
- Regarding the disclosure of protocol and study results and publication policy, references to the Coordinating Investigator were removed. No Coordinating Investigator was appointed on the study-wide level.
- A serious GCP breach definition was provided for clarity, and the terminology was updated from violation to deviation.
- The PedsQL questionnaires were added to Appendix A.

An Addendum, V4.0 – V1.0 for Sweden, dated 26 August 2020, was generated to introduce measures to ensure patient safety and counteract potential study conduct disruption during a COVID-19 outbreak.